Medical and Pediatric Oncology 28:268–273 (1997)

# Prior Fungal Infection Is Not a Contraindication to Bone Marrow Transplant in Patients With Acute Leukemia

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**Purpose:** Our aim was to assess the feasability of bone marrow transplantation (BMT) in patients with acute leukemia who have had prior documented invasive fungal infection within 5 months pretransplant treated aggressively with systemic amphotericin B and, when applicable, surgical resection of the infected tissue.
**Materials and Methods:** We reviewed the charts of patients with acute leukemia at our institution who underwent BMT between August 1992 and April 1994 after being treated for a severe fungal infection. We evaluated criteria for diagnosis of fungal infection, timing of infection in relation to BMT, and antifungal treatment modalities. We determined peritransplant complications, evidence for recurrence of fungal infection during BMT, morbidity related to antifungal drug therapy, and overall outcome in each patient.
**Results:** Fungal infection developed in eight patients. Sites of involvement included lung, liver, spleen, and skin. All patients were treated with systemic amphotericin B. Some also underwent surgical resection of infected tissue following clinical control of infection. All patients underwent BMT.
Seven of eight patients engrafted and survived BMT. One patient died of recurrent pulmonary mucormycosis. Three patients are alive and free of leukemia and fungal disease. Four patients died of noninfectious causes and had no evidence of fungal disease at the time of death.
**Conclusions:** Aggressive therapy of prior fungal infection followed by ongoing anti-fungal prophylaxis in acute leukemia patients may allow BMT without reactivation of the fungus. Reports of larger series of such patients as well as studies of the efficacy of chemoprophylaxis of fungal infections are needed. **Med. Pediatr. Oncol. 28:268–273.** 

**Key words:** systemic amphotericin B; surgical resection; antifungal treatment modalities

## INTRODUCTION

Patients with acute leukemia receiving chemotherapy are at risk for developing fungal infection [1]. Patients who relapse and/or undergo bone marrow transplantation (BMT) may have an increased risk of such infections as they are subjected to cycles of more intensive chemotherapy and prolonged periods of marrow aplasia [2]. Both diagnosis and treatment of mycotic infections can be difficult. Furthermore, even if the pathogen is eradicated, cancer patients have an increased risk of reactivation of the infection during subsequent courses of chemotherapy [2]. Recrudescence is especially problematic in patients undergoing BMT [3]. Nevertheless, successful transplantation without recurrence of mycotic infection has been reported in recent years [4–7]. We report our experience with acute leukemia patients who had a history of fungal infection within 3 weeks to 5 months immediately prior to undergoing BMT.

## MATERIALS AND METHODS

From August 1992 to November 1995, 30 patients who had been diagnosed with acute leukemia at the Children's Memorial Hospital (CMH) underwent BMT. Eight of these patients had documented fungal infections (confirmed by microbiologic or histopathologic evidence) prior to BMT (Table I). The age range of these eight patients was 11 months to 14.5 years. Four of the patients were girls and four were boys. All patients had acute leukemia (five acute lymphocytic leukemia [ALL], three acute nonlymphocytic leukemia [ANLL]). All patients received disease-appropriate intensive, myelosuppressive induction and consolidation chemotherapy prior to their ablative regimens for transplant.

Criteria for diagnosis of fungal infection included suggestive radiographic findings in the face of prolonged neutropenic fever refractory to broad-spectrum antibiotics with positive fungal cultures or histopathologic evidence of fungal elements. Fungal infection developed after consolidation chemotherapy for ALL relapse in five patients, after second remission induction of ANLL in one patient, and after first remission induction of ANLL in two patients. All patients had a history of fever and neutropenia and had been treated with broad-spectrum

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Received 19 September 1995; Accepted 6 May 1996

**TABLE I. Patient and BMT Characteristics**

| Patient | Age/sex | Disease status | Timing of infection[a] | Cycles of chemotherapy[b] | Delay of BMT (days) | Donor | Engraftment (day post-BMT)[c] WBC | Engraftment (day post-BMT)[c] Platelets |
|---|---|---|---|---|---|---|---|---|
| 1 | 12 yr/F | ALL: 2nd relapse | −4 mo | 3 | 121 | 3/6 matched mother | +13 | +13 |
| 2 | 5 yr/F | ALL: CR-2 | −1 mo | 1 | 15 | 6/6 matched full sibling | +56 | +72 |
| 3 | 7 yr/M | ALL: CR-2 | −5 mo | 4 | 153 | 6/6 matched half sibling | +52 | +168 |
| 4 | 11 mo/M | ANLL: CR-2 | −3 mo | 2 | 36 | 6/6 matched sibling | +20 | +20 |
| 5 | 7 yr/F | ALL: CR-2 | −4 mo | 4 | 103 | Autologous | +13 | +33 |
| 6 | 15 mo/M | ANLL: CR-1 | −2 mo | 1 | 0 | Autologous | +14 | +28 |
| 7 | 4 yr/F | ALL CR-2 | −3 mo | 4 | 70 | 4/6 matched father | — | — |
| 8 | 14 yr/M | ANLL: CR-1 | −3 wk | 0 | 0 | 6/6 matched full sibling | +19/+22 | +21/+36 |

[a]Time from onset of fungal infection to BMT.
[b]Number of cycles of chemotherapy given between diagnosis of infection and BMT.
[c]Engraftment criteria: ANC > $0.5 \times 10^9$/L, platelet count > $20 \times 10^9$/L independent of transfusion.

antibiotics prior to diagnosis of a fungal infection. In six patients, presumptive diagnosis of a fungal process was initially entertained on the basis of fever refractory to broad-spectrum systemic antibiotic therapy with suggestive radiographic findings; subsequently, microbiologic and/or pathologic findings confirmed the presence of infection (Table II). These six patients had fungal infection of a single organ or site (one spleen, one liver, four lung). Diagnoses in the other two patients were based on histologic examination of a skin lesion in one, which revealed fungal hyphae, and culture-proven *Candida albicans* infection of a lymph node and blood with concurrent multiple pulmonary nodules in the other.

All infections were treated aggressively (Table I). All patients received amphotericin B for 7 to 57 days and then every other day until neutrophil recovery post-transplant (range of days +13 to +56 post-BMT). The dosage for patients 1 through 7 was 1 mg/kg per day, while patient 8 received 5 mg/kg per day of liposomal amphotericin B. Six patients also recieved additional antifungal therapy (fluconazole 3–5 mg/kg/day IV or orally, itraconazole 200 mg per day orally, 5-flucytosine 100 mg/kg per day orally, or rifampin 20 mg/kg/day). Surgical resection of the known site of infection was performed in four patients, including splenectomy (patient 1), pulmonary right middle (patient 7) and right lower (patient 8) lobectomy, and resection of an eschar over an infected abrasion on one patient's leg (patient 2). Dose and frequency adjustments of antifungal drugs were made based on response to treatment and changes in renal function. The total dose of amphotericin administered ranged from 38 mg/kg to 111 mg/kg (555 mg/kg of liposomal amphotericin B for patient 8).

BMT was carried out in second complete remission in five patients, in first remission in two patients, and during second relapse (30% lymphoblasts in the bone marrow) in one patient (Table II). The interval between diagnosis of fungal infection and BMT ranged from 3 weeks to 5 months; one to four individualized cycles of additional chemotherapy were given to patients 1 through 7 during those time periods to maintain remission. Autologous transplant was performed in three patients; the remaining five received bone marrow from an human leukocyte antigen (HLA)-haploidentical parent, a parent matched at four out of six HLA loci, an HLA-identical full sibling, or an HLA-identical half sibling. Standard ablative chemotherapeutic regimens (cyclophosphamide, etoposide, and total body irradiation [TBI] or busulfan and cyclophosphamide with or without VP-16 were utilized. Routine supportive care included hospitalization in rooms with positive pressure unidirectional airflow systems, prophylactic acyclovir 250 mg/$M^2$/dose twice daily, IVIg 250 mg/kg weekly for the first 100 days following BMT and then monthly for 3 months, and broad-spectrum antibiotics for treatment of febrile neutropenia. Five patients (Nos. 2, 3, 5, 7, and 8) receive cytokines after bone marrow infusion to accelerate engraftment (absolute neutrophil count [ANC] greater than $0.5 \times 10^9$/L and sustained platelet count greater than $20 \times 10^9$/L; see Table I). The range of time to engraftment of neutrophils was 13–56 days post-BMT (median 19 days); for platelets it was 20–168 days (median 30 days). Patient 8 initially engrafted from days +19 to +21, but then experienced graft failure necessitating a second infusion of donor bone marrow on day +66; 36 days later, he achieved a second engraftment. Patient 7 had persistent fevers and tachypnea during her period of aplasia. A CT of the chest done on day +26 revealed extensive areas of bibasilar consolidation which was radiographically consistent with relapsed or (less likely) a second fungal pneumonia. She died of progressive pulmonary disease on day +27 with no evidence of marrow engraftment. Permission for post-mortem examination was denied.

All patients developed fever during the period of marrow aplasia. Bacterial or viral infections were documented in six patients (Table III), and all were successfully treated. Patients 1 and 2 developed new fungal infections which resolved after amphotericin therapy and

**TABLE II. Diagnosis and Treatment of Fungal Infection**

| Patient | X-ray | Micro | Pathology | Organism | Surgery | Total dose amphotericin | Additional anti-fungal agent | Baseline serum creatinine | Maximum serum creatinine |
|---|---|---|---|---|---|---|---|---|---|
| 1 | CT spleen | + | + | *Aspergillus* | Splenectomy | 94 mg/kg | Itraconazole | 0.4 mg/dL | 1.0 mg/dL |
| 2 | None | − | + | Unknown | Removal of eshcar from knee | 38 mg/kg | Fluconazole | 0.4 mg/dL | 0.8 mg/dL |
| 3 | CT chest | + | + | *Aspergillus* | Lung biopsy | 111 mg/kg | 5-FC/itraconazole | 0.4 mg/dL | 1.5 mg/dL |
| 4 | CT liver | − | + | *Aspergillus* | Liver biopsy | 95 mg/kg | 5-FC | 0.3 mg/dL | 0.6 mg/dL |
| 5 | CT chest | − | + | *Mucorales* | Lung biopsy | 82 mg/kg | — | 0.8 mg/dL | 1.1 mg/dL |
| 6 | CT chest | + | + | *Candida albicans* | Lymph node excision | 68 mg/kg | 5-FC | 0.3 mg/dL | 0.7 mg/dL |
| 7 | CT chest | − | + | *Mucorales* | Right middle lobectomy | 89 mg/kg | — | 0.5 mg/dL | 1.5 mg/dL |
| 8 | CXR, CT chest | − | + | *Aspergillus* | Right lower lobectomy | 111 mg/kg | Fluconazole, itraconazole | 0.2 mg/dL | 1.6 mg/dL |

**TABLE III. BMT Complications and Outcome**

| Patient | Infections | GVHD | Other complications | Outcome |
|---|---|---|---|---|
| 1 | *Alternaria* sepsis; oral herpes | Grade I liver | GI bleed, day +6 | Died, lymphoproliferative disease, day +93 |
| 2 | *Klebsiella* sepsis; cryptococcal meningitis, day +59 | Grade II skin, GI tract | Seizures, day +27 | Died, intracranial bleed, day +184 |
| 3 | Herpes zoster, L thigh | Grade I skin | None | Alive and well, day +921 |
| 4 | *Klebsiella* line sepsis; RSV | None | None | Alive and well, day +959 |
| 5 | None documented | None | Transient blindness, day +1 | Died, ALL relapse, day +324 |
| 6 | *Citrobacter* and *Pseudomonas* central line infections | None | None | Died, ANLL relapse, day +76 |
| 7 | Recurrent mucormycosis | None | None | Died, day +25 |
| 8 | *Klebsiella* pneumonia; *Strep. sanguis* sepsis | None | Graft failure requiring second infusion of donor cells | Alive and well, day +57/+123 |

were believed to be unrelated to the patients' prior histories of *Aspergillus* abscesses in the spleen and a single fungal skin lesion, respectively. Peritransplant complications other than infection included GI bleeding, seizures, and transient blindness, all thought to be unrelated to the prior fungal infections (Table III). Reversible renal toxicity (rising serum creatinine; Table II) developed in five patients during the transplant period and was managed by altering the dose or schedule of amphotericin administration. Repeat scans were done between days +16 and +118 post-transplant in all patients and showed no evidence of fungal disease, except in patient 7. Patient 4 had a central nervous system relapse of his ANLL on day +748. A third remission was achieved, and he received a second allogeneic transplant from his original donor. He had no evidence of recurrent fungal infection throughout the peritransplant period. He is now alive and off therapy without evidence of disease at day +959 from his first BMT. Patient 3 is alive and off therapy without evidence of disease, chronic GVHD, or fungal infection on day +921 post-BMT. Patient 8 is alive without evidence of leukemia or fungal infection at days +57 and +123 from his second and first donor marrow infusions, respectively. Four patients have died of noninfectious causes (two progressive disease, one massive intracranial hemorrhage, and one lymphoproliferative disease). Permission for post-mortem examination was granted only for patient 1, who had an examination limited to the chest and bone marrow; no histologic or microbiologic evidence of fungal disease was detected. None of the other three patients had clinical or laboratory evidence of recurrent fungal infection at the time of death. Only one patient died with presumptive recurrent fungus (pulmonary mucormycosis).

## DISCUSSION

Fungi have been widely recognized as the cause of serious infection in patients with hematologic malignancies with very significant morbidity and mortality [1,8–11]. The clinical picture of fungal infection may vary from superficial skin lesions to fungemias and/or disseminated organ infection. Diagnosis is often difficult because of problems in obtaining pre-mortem microbiologic isolates and of complications of invasive diagnostic procedures in neutropenic leukemic patients. Diagnosis may be made by culture, histologic evaluation of biopsied tissues, or presumptively on the basis of radiologic

findings in association with persistent fevers on broad-spectrum antibiotics [12,13].

*Candida* species are generally recognized as the most common fungal pathogens in immunosuppressed cancer patients [9,14,15] and are generally more responsive to amphotericin than noncandidal species [2,4,9,12,16,17]. *Aspergillus* species have become more prevalent and are especially significant because of their high mortality rate [3,9,18]. Other organisms such as *Mucormycoses, Fusarium,* and *Alternaria* have been reported in several series, and are perhaps associated with even greater mortality [4,9,16].

Standard treatment of fungal infections is systemic amphotericin B. The dose usually given is 0.6 to 1.5 mg/kg/day. Liposomal amphotericin B is amphotericin which has been encapsulated in liposomes for optimal uptake and distribution by the body; it is associated with significantly reduced toxicity and may therefore be administered in greater concentrations [19]. It has only recently become commercially available in the United States. Duration of chemotherapeutic antifungal therapy varies with the patient's response and overall clinical status. Surgical resection of affected tissue may also be necessary to control infection, especially if the organism is noncandidal [4,5,6,7,16,20]. Rifampin or flucytosine may provide a synergistic effect in some cases [21–23]. The less toxic triazoles are sometimes given prior to definite diagnosis or following initial amphotericin B therapy when appropriate.

Prognosis varies with the organism, extent of infection, primary disease status (remission vs. active disease), and recovery of peripheral blood neutrophils, and may be improved by early intensive treatment. The patients in our series developed mycotic infections after aggressive treatment of acute leukemia. All infections were confirmed by either culture or histologic evidence (Table II). Six patients had deep visceral infections, one of whom had multiple organ involvement and fungemia (patient 6). Patient 2 had a small eschar on the knee which, on microscopic examination, contained fungal hyphae; in the opinion of the pathologist examining this tissue, the most likely culprit was a Mucorales family member.

Although our patients had serious fungal infections with significant risk for a poor outcome, they all exhibited substantial improvement of fungal disease after an initial intensive course of full-dose daily amphotericin B. This excellent response is in marked contrast to previously reported outcomes in patients with noncandidal visceral mycoses [9,16,20].

The seven patients who received further chemotherapy after diagnosis of their fungal infections also continued to receive full-dose amphotericin every other day prior to BMT without recurrence of infection. Similarly, patient 8 received daily, full-dose liposomal amphotericin, which had just become available at our institution, until he underwent BMT without recrudesence of his pulmonary mucormycosis. This evidence of adequate control of infection increased our confidence that our patients might also tolerate BMT without reactivation of fungus. One or more of the known risk factors for development of fungal infection in BMT patients, including graft-versus-host disease, donor/patient mismatch, prolonged granulocytopenia, and preparation with total body irradiation, were present in five of our patients. Only one of these patients had probable recrudescence of her fungal infection, while the other four had no evident recurrence.

Significant undesirable side effects of amphotericin (i.e., renal toxicity) are common in patients who receive prolonged therapy [17]. Renal dysfunction is typically less severe in patients receiving liposomal amphotericin B [19]. Fewer side effects have been reported with triazoles, mainly mild reversible elevation of hepatic enzymes [24]. Although our patients received amphotericin for 3–7 months total, beginning from 1 to 5 months prior to BMT and continuing until leukocyte recovery or death with total doses of 38 to 111 mg/kg (555 mg/kg of liposomal amphotericin in patient 8), none experienced severe toxicity. Mild-to-moderate creatinine elevation occurred in five patients (Table II) but resolved after decreasing the dose or frequency of administration in the four patients who survived. Renal tubular acidosis requiring electrolyte supplementation occurred in two patients. O'Donnell et al. reported lower cyclosporine (CSA) levels in their BMT patients on amphotericin [25]. We noted lower CSA levels in two of five patients receiving the drug, although this was probably related to noncompliance in one of the patients. Amphotericin B has been associated with hepatotoxicity and myelosuppression, but these toxicities were not seen in our patients. Mild, transient elevation of liver enzymes associated with itraconazole occurred in patient 1.

Two patients developed new fungal infections in the peritransplant period. One patient grew alternaria from a single blood culture while she was febrile, aplastic, and receiving amphotericin every other day on day +7 post-BMT. Amphotericin B was intensified, and all repeat cultures remained negative. No further evidence of deep *Alternaria* infection was found on CT of the chest and abdomen, or on post-mortem examination and cultures. Clearly, this single positive culture could have been due to a contaminant, although the possibility of mild fungemia responding to therapy cannot be ruled out entirely. The other patient developed clinically evident cryptococcal meningitis on day +59, shortly after complete engraftment. Amphotericin, which had been discontinued 46 days earlier, was restarted, and subsequent CSF and blood cultures were negative for fungus. Her CNS infection was most likely unrelated to the skin lesion which

was removed and treated prior to transplant. This original lesion had none of the histologic characteristics of *Cryptococcus.* Furthermore, *Cryptococcus* rarely affects the skin, and is most often detected in the CNS and lungs [26]. *Mucorales* species, the presumed pathogen of her skin lesion based on histopathologic analysis, are often responsible for dermatologic and soft tissue infections. As described earlier, only one patient had clinical recrudesence of her mucormycosis, which ultimately caused her death. The other seven patients remained alive and free of fungal disease for +57 to +959 days.

Clearly, occurrence of fungal infection is an adverse event with significant associated morbidity and mortality. The high response rate to amphotericin B with minimal toxicity seen in these seven patients raises the issue of chemoprophylaxis of fungal infections in BMT patients. Several investigators have attempted to prevent infections with different agents including ketaconazole, miconazole, and low-dose amphotericin [3,27–29]. Results of these studies have been variable. There is clearly a need for prospective randomized studies of the value of prophylactic antifungal therapy as well as the optimal regimen in patients at high risk for serious fungal infection. Our results suggest that toxicity of amphotericin B, which is the ''gold standard'' treatment for deep-seated mycoses, may not be a hindrance to its use in a prophylactic setting, but its efficacy is not established.

## CONCLUSIONS

Although our patients had a history of fungal infection acquired during chemotherapy for acute leukemia, only one experienced recurrence of the infection during subsequent BMT. This suggests that prior fungal infection, even with deep visceral involvement, is not an absolute contraindication to BMT in pediatric patients with acute leukemia in remission if the infection has been controlled and/or eradicated. Obviously, such patients require aggressive therapy with amphotericin B, and perhaps surgical resection of infectious foci, prior to BMT. Furthermore, our experience would support the continued administration of amphotericin throughout transplant until neutrophil recovery. If side effects of amphotericin have become a problem and the infection appears to have resolved, a triazole may be given through and after BMT. Aggressive therapy may thus permit BMT which may be curative in some of these patients.

## ACKNOWLEDGMENTS

The authors are grateful to Charine Scott for assistance in preparation of this manuscript.

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